Justification for the amendments is as follows. The specification has been amended to correct inadvertent typographical and grammatical errors, and the claims have been amended to clarify the invention. In particular, the specification has been amended as the Examiner requested to update the status of the priority claim to a previously filed U.S. application. Claim 1 has been amended to delete the terms "substantially", "allelic variant" and "fragment". Claim 2 has been amended to recite a specific functional characteristic of a T-cell receptor protein, e.g., IL-2 inducing activity. Support for the amendment to claim 2 is found in the specification, for example, at page 50, Example X which describes an assay for measuring IL-2 induction in a cell transformed with TCRLP. Claim 13 has been amended to delete the terms "pharmaceutical", from "pharmaceutical composition", and the terms "substantially" and "suitable". New claims 24-26 have been added to claim additional methods of use of the polypeptides of the invention. Support for the new claims is found throughout the specification. For example, support for new claims 24 and 25 is found in the specification at page 42, lines 17-30, and at page 52, Example XIII (screening assays), and for new claim 26 at page 27, line 24 through page 29, line 3 (production of antibodies). No new matter is added by any of these amendments, and entry of the amendments is respectfully requested.

Objection to the Oath or Declaration

The Examiner stated that the oath or declaration is defective, and that a new oath or declaration in compliance with 37 CFR 1.67 (a) is required. Specifically, the Examiner stated, the oath or declaration is defective because (A) in the photocopy of the declaration provided to the office, the signature of the inventor Corley, as well as part of the address, have been cut off, and (B) the declaration does not include a claim to priority including U.S. Application No. 08/897,097 as disclosed in the specification.

With regard to item (A), Applicants have attached a new photocopy of the declaration from the parent application as required by 37 CFR 1.63(d). With respect to item (B). Applicants respectfully submit that the submission of a photocopy of the declaration from the parent application fully complies with the requirements of 37 CFR 1.63 (d). There is no requirement in 37 CFR 1.63 (d) for the oath or declaration in a continuation or divisional application to include a claim to priority of a previously filed parent application. Applicants therefore respectfully request withdrawal of the objection.

35 USC § 101, Rejection of Claims 1, 2, and 13

The Examiner has rejected claims 1, 2, and 13 under 35 USC § 101 because the claimed invention is not supported by a either a specific and substantial asserted utility or a well established utility. The Examiner directed Applicants to the Revised Interim Utility Guidelines, Federal Register, Vol. 64, No.

244, pages 71427-71440, Tuesday December 21, 1999.

The Examiner stated that the Applicant asserts a utility of the protein encoded by SEQ ID NO:1 as a pharmaceutical composition for the treatment or prevention of diseases ranging from autoimmune disorders to cancer, however that these are not substantial or credible utilities for the following reasons.

The utilities are premised on the similarity of the disclosed full length protein (SEQ ID NO:l) to a human T cell receptor beta chain taught by prior art. However, there is no recognition in the art that sequence identity predicts biological function and therefore a disclosure of sequence identity does not lead one of skill in the art to believe said identity gives a credible use to the claimed protein. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. teaches further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (see Abstract in particular). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al., teaches that a single Glu to Val substitution in the subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (see pages 126128, section 6-3A and page 230, paragraph bridging columns in particular).

Applicants respectfully disagree that the specification has not disclosed either a specific and substantial asserted utility or a well established utility. Applicants particularly disagree with the Examiner's statement that there is no recognition in the art that sequence identity predicts biological function. In support of the art recognized use of sequence homology to establish conservation of protein structure and function by species homology, Applicants have enclosed an article by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078; Exhibit 1). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Brenner et al. further report that at least 40% identity over at least 70 residues is also reliable in signifying homology between proteins (Brenner et al., page 6076). As shown in Figures 2A and 2B of the specification, TCRLP shares >80% identity with at least two known human

T-cell receptor proteins over at least 300 amino acid residues, vastly exceeding the criteria set by Brenner et al.

The Examiner has stated that it is well known in the art that even single amino acid changes can have dramatic effects on a protein's function, and has cited and discussed Mikayama et al. and Voet et al. in support of this contention. Applicants submit that the occurrence and/or propagation of such dramatic changes in nature is the exception not the rule. In support of this, the attached article by Bowie et al.(Exhibit 2) teaches that evaluating sets of related sequences, which are members of the same gene family, is an accepted method of identifying functionally important residues that have been conserved over the course of evolution. (Bowie et al., page 1306, 1st column, last paragraph, and 2nd column, 2nd full paragraph; page 1308, 1st column, last paragraph; page 1310, 1st column, last paragraph.) It is known in the art that natural selection acts to conserve protein function. As taught by Bowie et al., proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to occur. Conversely, mutations that reduce or abolish protein function are usually eliminated by natural selection. Based on these central tenets of molecular evolution, Applicants submit that the amino acid differences among Applicant's polypeptide and the known T-cell receptor proteins, are likely to occur at positions of minimal functional importance, while residues that are conserved are likely those that are important for protein function. One of ordinary skill in the art would therefore conclude that, more likely than not, the level of conservation observed between Applicant's polypeptide and the two known human T-cell receptor proteins is indicative of a common function, and hence common utility, among these proteins.

The Examiner's citation of Mikayama et al. in support of his position is of doubtful relevance for the following reasons. GIF and MIF are considered to be encoded by the same gene (Genbank NM 002415; g4505184; SWISSPROT P14174; Exhibit 3, attached). The cDNA sequence of MIF taught by Weiser et al. (Proc. Natl. Acad. Sci. 86:7522-7526, 1989; Exhibit 4, attached) differs from the sequence described and used by Mikayama by only one nucleotide base. No other artisans find this nucleotide base difference. Mikayama in fact states in his conclusions at page 10060, last paragraph, that "Since recombinant MIF has not been affinity purified, it is not conclusive that the 13-kDA peptide of the predicted amino acid sequence has the MIF activity. At present, however, the possibility cannot be excluded that a single amino acid difference between GIF and MIF may account for their biologic activities" (underline added). In fact, Weiser et al. later retracted their teachings using the MIF cDNA clone (Proc. Natl. Acad. Sci. 94:351; Exhibit 5, attached), having attributed the MIF biological activity to unauthorized addition of phytohemagglutinin to cell culture supernatants, and thereby invalidating laboratory experiments showing biological activity previously attributed to the Weiser MIF cDNA clone

(David J. Immunol. 151(9):Erratum, last page, unnumbered, 1993; Exhibit 6, attached). Therefore the conclusion that a single amino acid change converts GIF to MIF activity based on this one study is highly doubtful.

Likewise, the Examiner's citation of Voet et al. and the fact that a single amino acid change in hemoblobin causes sickle-cell anemia is again a case of the exception not the rule. The fact that the sickle-cell mutation has been perpetuated is a fluke of nature due only to the fact that it confers an advantage (immunity to malaria) in heterozygous carriers. Generally, without such coincidence, the sickle-cell gene would have been selected against, because it causes a disease that disadvantages the carrier. Without this extraordinary twist of fate, the mutant gene would have been eliminated many generations ago.

The totality of the evidence of record therefore does not support the Examiner's contention that one skilled in the art would conclude that, more likely than not, the differences observed between the amino acid sequences of TCRLP and the known human T-cell receptor proteins would affect the biological function of the protein. The now published Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday, January 5, 2001 state, specifically at page 1096, that the Examiner's decision to rebut Applicants assertion of utility:

> ---must be supported by a preponderance of all evidence of record (underline added). More specifically, when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the Examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. "[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient".

The Guidelines further state at page 1096:

> When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment (underline added) of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein.

Applicants have asserted a specific, substantial, and credible utility for polypeptides and antibodies specific to these polypeptides in the diagnosis, treatment, and prevention of cancers and autoimmune disorders based on the identification of TCRLP as most likely a new functional member of the T-cell receptor class of proteins, their known association with these disorders (see, in particular, specification, page 2, lines 26-30), and the predominant expression of the molecule in actively proliferating tissues of fetal origin and immune response tissues (specification, page 14, lines 23-25).

The evidence provided in the specification supports at least a reasonable correlation with this asserted utility. Applicants submit that the Examiner has not presented a proper *prima facie* case in rebuttal of this assertion based on the preponderance of evidence provided above, and respectfully request withdrawal of the rejection of claims under 35 USC § 101.

35 USC § 112, First Paragraph, Rejection of Claims 1, 2, and 13

This rejection as set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons. Applicants therefore respectfully request withdrawal of the rejection.

35 USC § 112, First Paragraph, Rejection of Claims 1 and 2

The Examiner has rejected claims 1 and 2 under 35 USC § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner stated that there is insufficient written description to show that Applicant was in possession of any variant of a peptide encoded by SEQ ID NO:1. Variant has not been defined in the specification, however "altered sequence" is defined to include peptides with any and all insertions, substitutions, and deletions, i.e., any peptide or protein. Variant is considered to include at least all "altered peptides", thus, one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See Eli Lilly, 119 F.3d 1559, 43 USPQ2d 1398.

Claim 1 has been amended to remove variant language. Claim 2, as amended, does not encompass any peptide or protein with altered sequence, but rather is limited to those having at least 90% amino acid sequence identity to SEQ ID NO:1, and which retain a specified biological function of a T-cell receptor protein, namely the ability to induce IL-2 activity. Applicants submit that this description is sufficient to describe the claimed genus based on the disclosure of the single species, SEQ ID NO:1, for reasons stated in the USPTO's own training materials for implementation of the Written Description Guidelines under 35 USC § 112, first paragraph. In the "Synopsis of Application of Written Description Guidelines" (USPTO Website www.uspto.gov, March 1, 2000), at page 53 of these guidelines, a claim to "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B" is considered to meet the written description requirements because:

--- procedures for making variants of SEQ ID NO:3 are conventional in the art

> and an assay is described which will identify all other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art.

The Guidelines further state:

> The single species disclosed (SEQ ID NO:3) is representative of the genus because all member have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity.

Applicants submit that claim 2, as amended, meets the written description requirement of 35 USC § 112, first paragraph for the same reasons, and respectfully request withdrawal of the rejection of claims 1 and 2 under 35 USC § 112, first paragraph.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections and rejections. Early notice to that effect is earnestly solicited. Applicants further request that, upon allowance of claim 1, that claims 24-26 be rejoined and examined as methods of use of the polypeptide of claim 1 that depend from, and are therefore of the same scope as claim 1, in accordance with *Ochiai and Brouwer*. See M.P.E.P. § 821.04 and the Commissioner's Notice in the Official Gazette of March 26, 1996.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent of Record.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108. This form is enclosed in duplicate.**

Respectfully submitted,

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